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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,802	02/09/2004	Kari Alitalo	28967/34891.1	9059

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EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,802	ALITALO, KARI	
	Examiner	Art Unit	
	IAN DANG	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,44 and 46-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,44 and 46-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 11 February 2008 has been entered in full. Claims 1-42 and 45 have been cancelled and claims 43, 46, 48, 49, 50, 53, 56, 61, 65, 67, 70, 71, 75, 80, 81, 82, 85, 86, 89, 90,91, and 94 have been amended. Claims 97 and 98 have been added.

Claims 43-44 and 46-98 are under examination.

Rejection Withdrawn

35 USC § 112, Second paragraph

Applicant's response and arguments filed on 02/11/2008 have overcome the rejection of claims 49, 53, 58, 61, 67, 71, 81, 85, 89, and 91 under 35 USC 112, Second paragraph. The rejection of claims 49, 53, 58, 61, 67, 71, 81, 85, 89, and 91 under 35 USC 112, Second paragraph has been withdrawn.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43, 44, 46, 49, 51, 52, 54-60, 61,-64, 71, and 76 remain rejected under double-patenting over claims 1-5, and 14-49 over US Patent No. 6,824,777. The reasons for this rejection are found at pages 3-13 of the previous Office action mailed 10/09/2007.

(i). At page 26 of the response, Applicants argue that all of the pending claims are directed to methods of inhibiting Flt4 function in a mammalian subject having a neoplastic disorder (or other disorder) characterized by expression of Flt4 in the blood vasculature (e.g., blood vessels, blood vascular endothelial cells, etc) of the subject. Some of the claims further include a specific method step involving, e.g., screening for a condition characterized by blood vessel expression of Flt4. (See, e.g., claims 53-60, 64-70, 87, and 89-93. The claims of the '777 patent do not recite such a method.

In addition, Applicants argue that the present claims are directed to an unobvious subgenus or species within the genus. For example, claims 43, 49, 53, 61, 65, 71, 81, 85, 89, 91, and those claims dependent thereon, require that the neoplastic disease (or other disorder) is characterized by expression of Flt4 in the blood vasculature (e.g., blood vessels, blood vascular endothelial cells, etc), a particular aspect not claimed in the '777 patent. As such, the pending claims 43, 49, 53, 61, 65, 71, 81, 85, 89, 91, and those claims dependent thereon, are not anticipated by the claims of the '777 patent.

Applicants' arguments and disclosure of Exhibit F have been considered but are not found persuasive. The Examiner is using the proper standard of review to assess double patenting between the claims of the instant application and those of the ‘777 patent. The Examiner agrees with Applicants that obviousness-type double patenting analysis only involves a comparison of the claims. However, the Examiner is required to refer to the specification of the '777 to determine the scope and breadth of the claims.

With respect to any additional method steps, the Examiner agrees with Applicants that the claims with additional method steps of inhibiting Ftl4 function in a mammalian subject, such as screening for a condition characterized by blood vessel expression of FLt4 (see claim 53) do not have any issues under double patenting with the claims of the '777 patent, since the claims of the '777 patent do not recite these steps. However, the recitation of "neoplastic disorder characterized by expression of Flt4 in the blood vasculature” in the claims of the instant applicant remains rejected under double patenting because the blood vascular endothelial cells and the expression of Flt4 in the blood vasculature are encompassed by the recitation of the claims for the '777 and would be an obvious variant of the claimed methods in the ‘777 patent.

Applicants argue that the breadth and the scope of the present claims are distinct from those of the parent's claims because specific embodiments, such as the disease breast carcinoma, the expression of Flt4 in vascular endothelial cells, or a polypeptide comprising an Flt4 binding fragment of human prepro VEGF-C, are not disclosed in the instant claims. For instance, claim 43 of the instant application recites a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease comprising administering to said mammalian organism a composition wherein neoplastic disease is a breast cancer characterized by expression of Flt4 in vascular endothelial cells.

Although the method of claim 1 of the ‘777 patent does not teach "wherein neoplastic disease is a breast cancer characterized by expression of Flt4 in vascular endothelial cells”, the neoplastic disease recited in claims 7 and 8 encompasses breast cancer, since neoplastic disease is a broad description for cancer and includes breast cancer. In addition, the neoplastic disease would inherently express Flt4, since claim 7 of the '777 patent recites that the neoplastic disease is characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells. Therefore, the claim 43 of the instant application cannot be considered distinct over claims 1, 7, and 8 of the '777 application because the invention of claim 43 is encompassed by the scope of the claims 1, 7, and 8 of the ‘777 and would be an obvious variant of the claimed method of inhibiting Flt4.

In addition, claim 61 is drawn to a method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising administering to said mammal a composition, said composition comprising an inhibitor of binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of: (a) an anti-Fit4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Fit4 antibody; (b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody; (c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody; (d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (e) a polypeptide comprising an Flt4 binding fragment of human prepro- VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

Although the method of claim 32 of the ‘777 patent does not recite "blood vessel endothelial cells”, the endothelial cell disease in 32 of the ‘777 patent encompasses the blood vessel endothelial cells of claim 61 of the instant application, because endothelial cells include numerous types of cells including blood vessel endothelial cells. In addition, the conjugation of an antineoplastic agent to the polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO:21) or a human prepro-VEGF-D (SEQ ID NO:22) of claim 31 is disclosed in claim 36 of the ‘777 patent. Therefore, the claim 61 of the instant application cannot be considered distinct over claims 32 and 36 because the invention of claim 61 is encompassed by the scope of claims 32 and 36 of the ‘777 and would be an obvious variant of the claimed method of treating a mammal having breast cancer.

(ii). At page 28 of the response, Applicants argue that claims 46, 50, 54, 62, 72, 73, 78, 82, 86, 90, 92, and those claims dependent thereon, require that the inhibitor for use in the claim-recited methods comprise a bispecific antibody that specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen. Such a bispecific antibody is not recited in any of the claims in the '777 patent. As such, claims 46, 50, 54, 62, 72, 73, 78, 82, 86, 90, 92, and those claims dependent thereon, are not anticipated by the claims of the '777 patent.

Applicants' arguments have been considered but are not found persuasive. Although the bispecific antibody is not disclosed in the ‘777 patent, the antibody of claim 46 would be an obvious variant of the antibody of claim 1 in the ‘777 patent.

For instance, claim 46 is drawn to a method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease, comprising administering to said mammalian organism a composition, wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells, wherein said

composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells of said organism, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

Although none of the claims of the '777 patent recite " a bispecific antibody", the antibody recited in claim 1 of the '777 patent encompasses the bispecific antibody recited in claim 46. The antibody in claim 1 inhibits Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism on vascular endothelial cells expressing Flt4. Therefore of the antibody of claim 46 would inherently bind inhibit Flt4 receptor because it also binds to vascular endothelial cells as the antibody recited in claims 1 and 7. While the antibody does not specifically bind to a blood vascular endothelial cell marker, the antibody of claim 1 of the '777 would be expected inhibit Flt3 receptor tyrosine kinase function because the antibody of the claim 1 of the '777 patent and the one of claim 46 of the instant application both bind to the blood vascular endothelial cells.

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-66 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At page 20 of the response, Applicants argue that the genus of compounds that are used in the methods of the claims is supported in the application by a fair and representative number of exemplary species and subgenuses of compounds, including anti-Fit4 antibodies and fragments thereof; anti-ligand antibodies and fragments thereof; soluble Flt4 fragments that will bind circulating ligand to prevent the ligand from binding Flt4 on cells; ligand fragments that bind but do not stimulate Flt4; and small molecules (See, e.g., specification at pages 15-16 and 77-78) Also, the application describes and enables binding assays to determine other compounds having the desired properties.

Applicants' arguments have been considered but are not found persuasive. Although Applicant discloses the biological activity for composition for inhibiting the Flt 4 mediated proliferation of Flt4 expressing cells utilized in the claimed treatment method in claim 65, Applicant has not provided any information regarding the identifying characteristics of the composition that can be used to inhibit Flt4 mediated proliferation in the claimed method. While the specification recites that the composition including a "compound effective to inhibit the binding of an Flt4 ligand protein to Fit4 expressed in cells of the organism" is meant any compound that inhibits the binding of the Fit4 ligand described herein as vascular endothelial growth factor C, as isolatable from PC-3 conditioned medium (page 13, lines 6-9), the claim fails to disclose any identifying characteristics of the composition that can be used to inhibit Flt4 mediated proliferation of Flt4 expressing cells in the claimed treatment method.

Therefore, Applicant has not satisfied the requirement for written description because the claimed composition of claim 65 encompasses a genus of composition but only identifying characteristics for anti-Flt4 antibodies and peptide or peptide fragments binding to Flt4. The specification does not provide any description of the special features of the composition, which are critical to inhibit Flt4 mediated proliferation of Flt4 expressing cells of the genus claimed.

Furthermore, the specification does not provide any teachings sufficient to one of skill in the art to isolate and identify the composition used the treatment method encompassed by the claims. Thus, Applicants have not provided any identifying characteristics or properties of the instant composition that would be expected to inhibit Flt4 mediated proliferation of Flt4 expressing cells such that one of skill would be able to predictably identify the composition encompassed by the instant claims.

Based on Applicants' disclosure and knowledge within the art, those of skill in the art would conclude that Applicants would not have been in possession of the claimed genus of composition that would be expected to inhibit Flt4 mediated proliferation of Flt4 expressing cells based on the disclosure of the species that include anti-Flt4 antibodies and peptide or peptide fragments binding to Flt4and relevant identifying characteristics. Thus, applicant was not in possession of the claimed genus and the written description requirement is not satisfied.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 65-66 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
Claims 65-66 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a neoplastic disorder in a mammalian subject, comprising (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian identified according to step (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, **to decrease**

Flt4 mediated proliferation of said Flt4-expressing cells, wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier does not reasonably provide enablement for a method for treating a neoplastic disorder in a mammalian subject, comprising (a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and (b) administering a composition to a mammalian identified according to step (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, **to inhibit** Flt4 mediated proliferation of said Flt4-expressing cells, wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Although Applicants have partially overcome the enablement rejection regarding the inhibitors of the binding between Flt4 ligand protein and Flt4 with the disclosure of Exhibits D and E, filed on 02/11/2008, the enablement rejection is maintained over the recitation of the inhibition of Flt4 mediated cell proliferation of Flt4 expressing cells and the composition used in the treatment method recited in claim 65.

The claimed treatment method remains enabled because it would require undue experimentation for one of skill in the art to treat a neoplastic disorder comprising the inhibition of Flt4 mediated proliferation with a composition. The term “inhibit” in claim 65 has been interpreted by the Examiner as meaning that an activity will not occur, i.e. the inhibition of Flt4 mediated proliferation of Flt4 expressing cells will not occur. However, Applicant has not provided any guidance or example for the method for treating a neoplastic disorder in a

mammalian subject comprising the inhibiting Fl4 mediated proliferation of Flt4 expressing cells by administering the a composition.

Finally, it would require undue experimentation for one of skill in the art to treat a neoplastic disorder comprising administering the composition recited in claim 65 because the specification does not provide any distinguishing characteristics the composition that can be used in the treatment method. In the absence of such a disclosure, a large amount of experimentation by trial and error will be required to determine the composition that can be used to treat a neoplastic disorder utilizing the claimed composition and one of skill in the art would not know how to use the claimed treatment method of the instant application.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IAN DANG whose telephone number is (571)272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
June 9, 2008

/David S Romeo/
Primary Examiner, Art Unit 1647